Lisa Merry

Why Doesn't a Pregnant Woman Reject her Fetus?

Recurrent Pregnancy loss (RPL) occurs when a woman has three or more consecutive miscarriages; this phenomenon happens in about 1-3% of women. Why some women reject their unborn fetus and others carry theirs to term is still unclear. There are four main theories that exist regarding why some women reject their fetus and others do not: the maternal immune system might not be capable of responding to fetal antigens due to mechanisms that induce tolerance in responding maternal cells; a "barrier" may from between mother and fetus, preventing access of maternal immune cell to fetal antigens; fetal cells may suppress the expression of their antigens; and the fetus may generate site-specific immune suppression. We will look closely at two studies that ask the questions: does the non-specific immune response increase to compensate for the decrease in specific immunity? Is there a maternal cell-mediated immune response to the fetus which needs to be blocked, and do blocking antibodies develop in all successful pregnancies? Different aspects of each theory have proven that a maternal cell-mediated response is not acquired at any stage in pregnancy to the fetus but monocyte surface expression is increased. This proves that there is an increase in the innate immune response. Future studies will look more strictly at the differences between these main theories.

Background

Pregnancy has become a lot safer than in the past due to technology in medicine and a higher level of education for our health care professionals. Still little is known as to why pregnancies for some women are successful and for other women they are not. 50-60% of pregnancies have a common complication called spontaneous miscarriage, defined as the spontaneous end of a pregnancy that occurs prior to 20 weeks gestation where the embryo or fetus is incapable of surviving; a less common form of miscarriage is recurrent pregnancy loss, or RPL, which occurs in 1-3% of women and is defined as three or more consecutive miscarriages prior to 20 weeks gestation (Saini V., et al. 2011).

There are four different theories experts have studied to understand why this occurs. First, due to mechanisms that induce anergy, reduction or lack of an immune response to a specific antigen, the maternal immune system might not be capable of responding to fetal antigens (Koch and

Platt 2007). Second, an anatomical barrier may form that prevents access of maternal immune cell to fetal antigens between mother and fetus (Koch and Platt 2007). Third, fetal cells may suppress the manifestation of alloantigens; an alloantigen is any antigen, present in only some individuals of a species, which stimulates the production of antibodies in those that lack it (Koch and Platt 2007). Finally, the fetus may create site-specific immune suppression in which maternal immune cells would then be blocked, defending the fetus while permitting the cells to produce an immune response (Koch and Platt 2007).

In a normal pregnancy the immunological recognition of the fetus is important so that both the innate and the adaptive immune responses can work together to maintain gestation (Aagaard-Tillery, et al. 2006). The adaptive immune response uses t-cell recognition to promote either cell-mediated or humoral immunity depending on the antigen. B- Lymphocytes are first generated at 8-12 weeks human gestation in the fetal liver and are involved in both cell-mediated and humoral immunity (Aagaard-Tillery, et al. 2006). There are two stages of B-cell differentiation: ‘antigen-independent’ and ‘antigen-dependent'; ‘antigen-independent’ is a cell that is capable of responding to an antigen and ‘antigen-dependent’ occurs after a cell is exposed to an antigen (Aagaard-Tillery, et al.2006). T-Lymphocytes are associated with cell-mediated immunity and can be found in the lymph. T-cells that recognize antigens presented with class II MHC molecules are CD+4 cells and t-cells that recognize antigens presented with class I MHC molecules are CD8 cells (Aagaard-Tillery, et al. 2006). MHC determines the ability to tolerate tissue grafts and in humans is referred to as HLA, human leukocyte antigens (Aagaard-Tillery, et al.2006).

The innate immune response keeps the body safe by barriers such as the skin and mucous membranes and non-specific cells such as macrophages, natural killer cells, and neutrophils (Aagaard-Tillery, et al. 2006). The primary functions of these non-specific cells are to migrate, chemotax, ingest, and destroy microbes (Aagaard-Tillery, et al. 2006). Natural killer cells may also play a key role in a normal pregnancy given that 50-90% of leukocytes in the decidua are NK cells a place where T and B cells are rare (Aagaard-Tillery, et al. 2006).

At the maternal-fetal interface LGLs, large granular lymphocytes and macrophages are present (Aagaard-Tillery, et al. 2006). The number of LGLs increases throughout the first stage of pregnancy until they are the most abundant lymphocyte in the decidua and are then decreased by mid-trimester (Aagaard-Tillery, et al. 2006). It is speculated that LGLs use cytokines to limit

trophoblast invasion or to destroy damaged cells (Aagaard-Tillery, et al. 2006). Macrophages are the predominant leukocyte and persist as pregnancy advances (Aagaard-Tillery, et al. 2006). Macrophages are most abundant at the placenta that could play a role in pregnancy maintenance (Aagaard-Tillery, et al. 2006).

Cytokines may play an important role in a normal pregnancy but much is still unknown. Cytokines do appear in normal pregnancy and it is guessed that harmful levels may be produced in certain conditions such as RPL, but it is also suggested that cytokines may act as placental growth factors that lead to the fetal survival, which is known as the theory of immunotrophism (Aagaard-Tillery, et al. 2006).

The first theory that certain mechanisms induce anergy and the maternal immune system might not be capable of responding to fetal antigens suggests that the uterus is not an immune privileged site (Koch and Platt 2007). Studies have shown that during pregnancy the maternal immune response changes (Koch and Platt 2007). In the 2nd and 3rd trimester CD4+ T-cells decrease and in the third trimester CD8+ T-cells decrease; that proves that the amount of T-cells during pregnancy, specific for the fetus, can change dramatically (Koch and Platt 2007). This suggests that maternal T-cells recognize fetal antigens (Koch and Platt 2007).

The second theory, the idea that an anatomical barrier exists between mother and fetus, suggests that a barrier formed by the trophoblast separates mother and fetus from multiple different cell types (Koch and Platt 2007). The trophoblast produces their own cells called synctiotrophoblast and they can resist an immune attack from the mother (Koch and Platt 2007). If an immune injury does occur, it can be repaired quickly because the cells of the trophoblast are being constantly renewed (Koch and Platt 2007). One study shows that trophoblast cells can resist attack by CD+8 cells whereas normal cells of the fetus do not (Koch and Platt 2007). It is also hypothesized that the maternal immune system cannot contact fetal cells that hold the alloantigen due to the maternal-fetal barrier; this is termed the maternal-fetal chimerism (Koch and Platt 2007). Still, some cells do enter the maternal blood and can live for years or even decades in the mother without harm; and although chimerism can induce tolerance, maternal-fetal chimerism appears not to do so (Koch and Platt 2007). A study in mice by Tafuri, et al. shows that mice were tolerant but only for a short time (Koch and Platt 2007). The role of maternal-fetal tolerance still remains unclear.

The third theory, suppression of fetal antigens during pregnancy, suggests that by suppressing the expression of fetal alloantigens, fetal cells might avoid detection by the maternal immune system (Koch and Platt 2007). Trophoblast cells do not express either MHC class I or II molecules and this lack of expression might help explain why the fetus survives in the hostile environment of the mother's immune system, although this does not completely explain why the fetus has the ability to avoid ruin by the maternal immune system (Koch and Platt 2007). A study by Rogers, et al. induced the expression of MHC class molecules on trophoblast and the maternal immune system did not reject the fetus, thus the fetus is protected from the maternal immune system by other mechanisms as well as by immunological ignorance (Koch and Platt 2007).

The final theory, site-specific suppression, is the most complex and least understood. The immune system is a multiparty system and it is not fully understood exactly how those parts are intertwined with each other to ensure the health of the unborn fetus. There are four main parts of the immune system that scientists are looking at to prove site-specific suppression: Fas/FasL pathway, Tryptophan catabolism, HLA-G, and the cytokine environment (Koch and Platt 2007). The theory of site-specific immune response allows for full action of the immune system to allow for maternal immune defense while still promoting the immune system of the fetus (Koch and Platt 2007).

Fas/FasL induces apoptosis, cell death, which is essential to the immune system as evidenced by when this pathway is disrupted it causes severe autoimmunity (Koch and Platt 2007). FasL induces apoptosis of cells who have the Fas receptor this pathway is thought to be important at the maternal-fetal interface to help control the maternal immune response to the fetus (Koch and Platt 2007). Cell death is detected at all stages of fetal development; this may reflect normal death of cells in an area of high proliferation (Koch and Platt 2007). However, it is hypothesized that it may also stop the maternal immune system from attacking the fetus (Koch and Platt 2007). A study by Coumans, et al. found that CD3+ cells suffer apoptosis when cultivated with cells of the trophoblast due to FasL (Koch and Platt 2007). This may prove that FasL interactions are essential for the removal of maternal T-cells that are harmful to the fetus (Koch and Platt 2007). Although, mice that are deficient in Fas/FasL are still able to reproduce which suggests that it is not essential for the survival of the fetus (Koch and Platt 2007).

The maternal immune response to the fetus is thought to be inhibited by the catabolism of tryptophan (Koch and Platt). A study by Munn, et al. gave mice carrying an allogenic fetus an

enzyme that catabolizes tryptophan which therefore caused the mice to abort their fetuses (Koch and Platt 2007). Tryptophan levels decrease during pregnancy compared to un-pregnant woman whose levels remain unchanged (Koch and Platt 2007). Tryptophan also aids in the inhibition of T-cells and B-cells and prevents their activation and proliferation; tryptophan catabolites cause apoptosis of T-cells (Koch and Platt 2007). The act of tryptophan in mice is essential in maintenance of the pregnancy but still little is known about its act in human pregnancy (Koch and Platt 2007). Studies involving tryptophan are near impossible to do, given the risk of causing a fetus to be aborted. It's hypothesized that tryptophan plays a role in a successful human pregnancy by using a combination of its properties (Koch and Platt 2007).

HLA-G was originally thought to protect the fetus from NK cell damage, but it is hypothesized that it may also aid in protecting the fetus from T-cell-mediated damage (Koch and Platt 2007). A study by Riteau shows that cells with HLA-G inhibit up to 95% of T-cell growth in mixed cultures (Koch and Platt 2007). How HLA inhibits this response is still unknown.

The cytokine environment plays a very important role in human pregnancy although little is known about what mechanism is the key to a successful pregnancy. Cytokines are produced by trophoblastic cells in the decidua which includes mainly T-cells (Saini V., et al. 2011). Th-1 cells produce (IL)-2 and (IFN) whereas Th-2 cells produce IL-4, IL-5, and IL-13 (Saini V., et al. 2011). It's theorized that an increased Th-2 type environment is essential for a successful pregnancy and if a Th-1 type environment becomes dominant it results in an aborted fetus (Saini V., et al. 2011). Th-1 cells and the cytokines they produce are responsible for cellular immunity whereas Th-2 cells and the cytokines they produce are responsible for antibody production (Saini V., et al. 2011). Th-2 cytokines are thought to be more abundant at the maternal-fetal interface as they subdue cytotoxicity if there is an overstimulation of Th-1 it could lead to abortion; therefore a balance between Th-2 and Th-1 is needed for a successful pregnancy (Saini V., et al. 2011). Hormones may play a role in the production of more or less Th-2 or Th-1 cytokines, progesterone and luteinizing hormone may affect the cytokine environment at the maternal-fetal interface (Saini V., et al. 2011). Other cytokines that may play a role in pregnancy include IL-23, IL-6, and IL-10 (Witkin, et al. 2010). IL-23 produces an immunity defense against microorganisms that enter amniotic membrane, if its defense cannot defeat the infection IL-23 triggers the production of cytokines that will then trigger preterm labor (Witkin., et al. 2010). IL-6 is essential for anti-inflammatory purposes and the production of IL-6 is in response to

microorganisms (Witkin, et al. 2010). IL-6 benefits the health of the fetus as it protects it from infection but like IL-23 if it cannot fight off the infection it triggers cytokines to induce preterm labor (Witkin, et al. 2010). IL-10 blocks the cell-mediated immune response by inhibiting the production of Th-1 cytokines (Witkin, et al. 2010). IL-10 is also released to prevent extreme inflammation that could reach a damaging level to the fetus.

These four theories are being rigorously studied to determine the cause of healthy pregnancies in woman versus woman who have had 3 or more miscarriages. If these theories could be proven it could lead to a much better understanding of our immune system when it is fighting off a foreign object with different antigens. This could potentially lead to a new method of tissue grafting that wouldn't involve immunosuppressant drugs. It could lead to a new age of reduced organ rejection following organ transplants.

Adaptive Immune Response

Three or more consecutive miscarriages a condition known as RPL is seen in 4-8% of pregnant women and in 30-50% of these cases why the women miscarriage is still unknown (Sargent, et al. 1988). It is theorized that these recurrent miscarriages are caused by the maternal immune system rejecting the semi-allogeneic fetus (Sargent, et al. 1988). This has been treated with immunosuppressant drugs but this treatment is based fully on circumstance and little is known if it has any effect (Sargent, et al. 1988). There are two main concepts essential for the understanding of immunosuppressant drugs. One being that there is a maternal cell-mediated immune response to the fetus that needs to be blocked and two being that blocking antibodies develop in successful pregnancies (Sargent, et al. 1988). The understanding is that if there is a lack of these antibodies it results in the rejection of the fetus by the maternal immune system (Sargent, et al. 1988). This study by Sargent, et al. searches for the answers to these assertions.

An experiment was conducted on 37 women where a variety of measurements were taken on both the women once they became pregnant and their husbands (Sargent, et al. 1988). 27 women with a history of recurrent pregnancy loss with the same husband, not currently pregnant, and no cause that could be found for abortions and ten women embarking on their first pregnancy as a control group were studied (Sargent, et al. 1988). Both patients and controls were seen twice for baseline measurements before they became pregnant and were asked to report back to the clinic as soon as they missed their first period and an at home pregnancy test affirmed a pregnancy

(Sargent, et al. 1988). At 5-8 weeks blood was draw for immune testing which was then repeated at 9-12 weeks and 13-17 weeks of development. The life of the fetus was monitored and if fetal death occurred they would abort the fetus and immune testing would be repeated immediately afterwards (Sargent, et al. 1988). At the first visit of the husband to the clinic blood was drawn and put in to test tubes for tissue typing and the mononuclear cells were separated for mixed lymphocyte reactions or MLR (Sargent, et al. 1988). Cultures containing the woman's blood and also either the husband's blood or unrelated blood were measured for proliferation for six days; thymidine was then added and after 18 hours the cultures were harvested (Sargent, et al. 1988). Tissue typing for HLA A, B, C and DR and cytotoxic T and B cells were also measured (Sargent, et al. 1988). Pregnancy serum as a blocking factor was also measured along with direct cytotoxicity (Sargent, et al. 1988).

Of these 27 women who had a history of RPL, 18 became pregnant, the average age was 31 years old and 12 had not had a live born baby and had had an average of four miscarriages (Sargent, et al. 1988). The other six had had one live child and an average of four miscarriages (Sargent, et al. 1988). The average time taken to become pregnant once the study began was 29 weeks roughly one year after the last miscarriage (Sargent, et al. 1988). Of these 18 women who were successfully pregnant nine had an effective pregnancy at term and nine had first trimester miscarriages, all were genetically normal (Sargent, et al. 1988). The ten controls became pregnant roughly between 2-41 weeks after the study began average time being 17 weeks. Seven had normal deliveries at term, two had miscarriages, and one had proteinuric pre-eclampsia (Sargent, et al. 1988). These three women were excluded from the analysis (Sargent, et al. 1988).

The seven controls and the nine women in the study who had successful pregnancies MLR maternal with paternal were identical (Sargent, et al. 1988). On day six the responses reached a maximum, both before pregnancy and at 5, 9 and 13 weeks development (Sargent, et al. 1988). The nine women who had miscarriages, their MLR were significantly lower to both maternal with paternal and maternal with unrelated than those of women with a healthy pregnancy (Sargent, et al. 1988). There was no significant cytotoxicity against either unrelated target cells or paternal cells before pregnancy or at 5, 9, 13 weeks of development in both successful pregnancies and in the controls (Sargent, et al. 1988). For those women who miscarried, in the six women with recurrent miscarriage paternal-specific cytotoxic T-cells were not detected (Sargent, et al. 1988). The three women in the control who had miscarriages, there was a strong

paternal-specific cytotoxic T-cell response (Sargent, et al. 1988). One of these women in the control gave a strong reaction against the unrelated control, the husband and the control were HLA-DR incompatible but they shared HLA A and B (Sargent, et al. 1988).

In the study of serum blocking of MLR both the controls and patients with successful pregnancies had similar results (Sargent, et al. 1988). Before pregnancy there was a blocking index greater than one (Sargent, et al. 1988). As pregnancy continued, the blocking serum decreased to .8 at around 13 weeks development (Sargent, et al. 1988). This decrease was not statistically significant and was non-specific (Sargent, et al. 1988). The women who miscarried during the study showed a similar sera and depiction to those with successful pregnancies (Sargent, et al. 1988).

There were no significant differences between those women who miscarried and the women who had successful pregnancies in cytotoxicity or in a blocking serum. This proves that the mother does not acquire a cell-mediated immune response during any stage in pregnancy to the fetus (Sargent, et al. 1988). This also proves that there is no cell-mediated response to any fetal paternal HLA (Sargent, et al. 1988). No cytotoxic antibodies to paternal HLA or maternal cell-mediated immunity developed consistently during early fetal development, and there was therefore no correlation between the blocking serum and the success of a pregnancy (Sargent, et al. 1988). Thus recurrent pregnancy loss or spontaneous abortion is not caused by a cell-mediated immune response to fetal paternal HLA. There are two major limitations to this study. One being that the immune responses in the blood must accurately represent local activity in the uterus and it is only an observational study and they cannot account for any secondary effects (Sargent, et al. 1988).

The theory that an anatomical barrier or a “blocking factor” forms between mother and fetus that prevents access of maternal immune cell to fetal antigens is proposed as a necessary feature to all successful pregnancies. During pregnancy most sera non-specifically inhibits MLR, if this blocking factor is not present it may lead to abortion (Sargent, et al. 1988). However, there is not much support for this theory seeing as in both women with recurrent abortion and women with successful pregnancies cytotoxic antibodies are not usually present during the first trimester when miscarriages are most common. Cytotoxic T-cells still may be one the causes of recurrent pregnancy loss. Three of the nine women who aborted had circulating cytotoxic cells at miscarriage (Sargent, et al. 1988). This may prove that there is more than one cause for abortion.

All of the women in the study had unexplained miscarriages and therefore there could be many different causes for why it happens and not singularly an immune response to the fetus due to paternal HLA. The presence of T-cell suggests that an immune reaction may cause spontaneous miscarriages in some cases (Sargent, et al. 1988). As of this study, there had been no other human investigations for maternal-cell mediated immunity to the fetus (Sargent, et al. 1988). The only evidence to fully support this study was that there was an appearance of cytotoxic T-cells at miscarriage for three women (Sargent, et al. 1988). Unfortunately, three women are not statistically significant for proving a hypothesis.

Innate Immune Response

During pregnancy a hypothetical balance must exist between the host's immune system and prevention of the foreign fetus from being rejected by that immune system (Davis, et al. 1998). Some immune functions are therefore decreased during pregnancy and a mechanism that compensates for this decrease may exist in which other parts of the immune system increase (Davis, et al. 1998). Davis, et al. proposes that non-specific immunity or the innate immune response is increased to make up for the decrease in specific immunity to sustain adequate maternal host defense (1998). They believe that monocyte-macrophages play a key role in the immune system during pregnancy, linking both specific and non-specific responses by three classes of Fc gamma receptors that are present on monocytes: CD64, CD32, and CD16 (Davis, et al. 1998). The five functions facilitated by Fc gamma receptors are its participation in antibody dependent cell-mediated cytotoxicity, triggering of phagocytosis, release of TNF-α, release of IL-6, and production of reactive oxygen intermediates (Davis, et al. 1998). Monocyte numbers increase throughout pregnancy along with a heightened capacity for them to migrate around the body and ingest more foreign substances (Davis, et al. 1998). This may prove that not only does monocyte numbers increase but they also increase in function (Davis, et al. 1998).

This study by Davis, et al. was conducted to determine if there was an increase in CD64 and CD32 of monocytes throughout pregnancy that could be generalized for all women (1998). An experiment was then conducted using blood from both healthy non-pregnant women and healthy pregnant woman in at least one of the three trimesters; the non-pregnant women as the control and the pregnant women as the subjects (Davis, et al. 1998). Peripheral blood was drawn from all of the volunteers; 8-10 healthy pregnant women during one of the three trimesters 21-39 years of

age and the control subjects were age-matched, premenopausal (Davis, et al. 1998). The blood was then placed in to test tubes and added to different monoclonal antibodies (Davis, et al. 1998). The antibodies were then mixed with FITC or PE to determine Fc gamma receptor expression (Davis, et al. 1998). The cells were then washed to remove any unbound antibodies and they were then exposed to hypotonic lysis to remove all the red blood cells (Davis, et al. 1998). Peak channels of CD64 and CD32 were recorded on a light scattergram (Davis, et al. 1998). The phagocytic capacities of monocytes in pregnant women were measured by the ingestion of anti-D-sensitized human Rh-positive red blood cells (Davis, et al. 1998). The monocytes were isolated and then the blood was separated by density and placed in to petri dishes (Davis, et al. 1998). Slides of the monocytes were created and then coded and using a light microscope examined for ingested red blood cells (Davis, et al. 1998). Using an independent t-test the mean values of the test groups were compared with those of the control group (Davis, et al. 1998).

Fc gamma radiation CD64 and CD 32 surface expression were measured in pregnant women and in a non-pregnant control group using antibodies against CD64 and CD32 (Davis, et al. 1998). The results, represented by mean channel fluorescence, show a continued significant increase in the expression of CD64 throughout the three trimesters of pregnancy (Davis, et al. 1998). Throughout the three trimesters of pregnancy there was also a continued significant increase in the expression of CD32 (Davis, et al. 1998). HLA-DR was also measured to evaluate the activation state of the monocytes as the monocytes may exhibit Fc gamma radiation expression when they become activated (Davis, et al. 1998). The results show that there was no significant change in HLA-DR expression in either the control group or the pregnant subject group (Davis, et al. 1998). The results, according to an antigen quantitation kit, also show that there was a significant increase CD64 ABC as it was found in all three trimesters compared to the non-pregnant control group (Davis, et al. 1998). CD64 ABC represents the antibodies bound to the cellular surface and in each trimester it increased from 37.9 to 87.4 and then to 105.3% (Davis, et al. 1998). There was also a statistically significant increase in CD32 ABC with increases from 18.6 to 24.9 and then to 33.4% (Davis, et al. 1998). CD32 ABC increased at a lesser pace than those of CD64 ABC expression. During pregnancy, monocyte surface Fc gamma radiation increases (Davis, et al. 1998). Other studies show that this increase in expression results in increased Fc gamma radiation functions (Davis, et al. 1998). Davis, et al. uses monocytes from pregnant women to assess their ability to ingest anti-D-sensitized human Rh-positive red blood

cells to confirm or deny if Fc gamma radiation functions are increased by an increased expression of Fc gamma radiation (1998). The primary values represent a good means of measuring Fc gamma radiation-mediated function (Davis, et al. 1998). These results prove that phagocytic monocytes in all three trimesters of pregnancy increase as compared to the non-pregnant control group (Davis, et al. 1998). The total number of red blood cells ingest per 200 monocytes was also determined by this experiment. Davis, et al. found that during all three trimesters here was a significant increase in the phagocytic index compared to the non-pregnant control group.

This study proves that there is an increase in both CD32 and CD64 expression along with an increase in the phagocytic ability of monocytes during all three trimesters of pregnancy. The results also show that there was no significant change in HLA-DR in either the subjects or the control group (Davis, et al. 1998). There was also increase in antibodies bound to the cellular surface of both CD32 and CD64 expressions. There are at least three different Fc gamma radiation expressions that can bind to different receptors. These receptors allow for immunocompetent and inflammatory cells to interact with antibodies or antigens due to the receptors unique distribution patterns (Davis, et al. 1998). This allows for the regulation of the immune system (Davis, et al. 1998).

Fc gamma radiation expression may play an important role between adaptive and innate immune responses although much is still unknown (Davis, et al. 1998). This study shows that there may be an increase in the phagocytic capability of the cells due to an increase in Fc gamma radiation expression (Davis, et al. 1998). Davis, et al. .'s findings show that there is a constant increase in Fc gamma radiation expression throughout pregnancy in both CD32 and CD64 expression (1998). If it is true that there as an increase in both phagocytosis and an increase in Fc gamma radiation expression these results would be able to argue that non-specific or the innate immune response is enhanced during pregnancy to allow for the health of the fetus (Davis, et al. 1998). This may then prove that the mechanism that allows for the pregnant host to both fight infection but maintain the health of the fetus is due to an increase in non-specific or the innate immune response (Davis, et al. 1998). This data also supports the theory that Fc gamma radiation expression results in an increase of phagocytosis, which is an innate immune response (Davis, et al. 1998). Davis, et al. can then conclude that his hypothesis that non-specific immunity is increased during pregnancy due to the increase of phagocytic capability by the monocytes

(1998). These results speculate that there is an increase in the innate immune response to make up for the decrease in the adaptive immune response to allow for the overall health of the fetus but still more studies need to be done to approve this hypothesis.

Discussion/Conclusion

Why some women suffer from recurrent pregnancy loss and spontaneous abortions and other women do not is still unknown. Many theories have been questioned and studied but there is still no concrete answer. The immune system is so complex; it is difficult to figure out the exact mechanics of how the semi-allogeneic fetus survives in such a harsh environment of the maternal host. Davis, et al. proves that there is some inhibition of the cell-mediated immune response and an increase in the innate immune response (1998). Sargent, et al. rejects the idea that the women suffering from RPL have a sensitized cell-mediated response directly to the fetus (1988). Other studies have also been done that show similar results on both animals and humans. I believe that these studies prove that there is more to a successful pregnancy than just one theory.

I think it is a very complex series of events that allow the fetus to remain unharmed in a hostile environment. I think that the next approach taken by scientists looking to discover the cause of spontaneous abortion should test each theory and find a way to explain it using aspects of the different theories. I believe that it such a complex system that no one part of the immune system can account for the safety of the fetus and that several components likely play a role in the health of the developing foreign fetus. The immune system it so complex it may be impossible to ever fully understand why some women have spontaneous miscarriages and other women do not.

If this question could be solved it would not only help women have more successful pregnancies, it would allow us to use the information we uncover about the immune system to use in different parts of medicine. Not only could we save the life of the fetus, we could save many lives with a new method of successfully transplanting organs. If we can fully understand how the immune system works to allow the growth of a foreign fetus we can use this method to allow for the growth of a foreign organ in the body. With this kind of information we could cut the risk of rejecting a transplanted organ down substantially. The question of why doesn't a pregnant woman reject her fetus is one that should be studied regardless of whether we can ever pinpoint an answer.

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